REMARKS

The Official Action dated August 5, 2010 has been carefully considered. Accordingly, it is believed that the present Amendment responds fully to the outstanding matters and places this application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claim 1 is amended to include limitations from claim 3, and to describe an embodiment of the multilayer structure in which a portion of the vesicles are attached to the structure by binding vesicle-attached linkers to vesicle-attached linkers of other vesicles, as shown in Fig. 2 and described in the specification in the paragraph bridging pages 20 and 21. Claim 1 is also amended to recite that at least a selected population of the vesicles comprise a biologically active compound which provides the structure with biological functionality, in accordance with the teachings of the specification at pages 23-24. Claims 2, 3, 12 and 35 are cancelled, and claims 6, 13, 15, 17-21, 33 and 61 are amended to change their dependency from a cancelled claim to a pending claim, to correspond with claim 1 as amended, and/or for a matter of form. It is believed the present changes do not involve any introduction of new matter, whereby entry is in order and is respectfully requested.

Claims 1, 5-11, 13, 15, 17-22, 33, 34, 36, 37, 39 and 41-65 are pending. Applicants request rejoinder of claims 6, 7, 9-11, 13, 15, 17-22, 33, 34, 36, 37, 39 and 41-62, which all depend directly or indirectly from claim 1, upon allowance of claim 1.

In the Official Action, claims 1 and 65 were rejected under 35 U.S.C. §102(b)as being anticipated by the Patolsky et al, *Journal of the American Chemical Society*, 123:5194-5205 (2001). The Examiner asserted that Patolsky anticipates the claims by teaching in Scheme 1A a liposome with oligonucleotide (3) interacting directly with a double stranded assembly formed

on a surface, resulting in immobilized liposome with biologically active oligonucleotides. The Examiner referred specifically to page 5196, Results and Discussion.

This rejection is traversed with respect to present claims 1 and 65, and reconsideration is respectfully requested. That is, according to claim 1, the invention is directed to a biologically-functional, surface-immobilized multilayer structure comprising a plurality of vesicles sufficiently spaced apart from the surface. A portion of the vesicles are directly attached to the structure by binding surface-immobilized linkers with vesicle-attached linkers and a portion of the vesicles are attached to the structure by binding vesicle-attached linkers to vesicle-attached linkers of other vesicles, so as to provide the structure with two or more vesicle layers. The surface-immobilized linkers and the vesicle-attached linkers comprise oligonucleotides and binding of one linker to another linker is mediated through hybridization of the linker oligonucleotides. At least a selected population of the vesicles comprise a biologically active compound which provides the structure with biological functionality.

Patolsky discloses that in Scheme 1A, a probe oligonucleotide (1), complimentary to a target analyte DNA (2) is assembled on a transducer and in the presence of the analyte, a double-stranded assembly is formed on the surface. The resulting assembly is then interacted with an oligonucleotide (3)–functionalized liposome component, wherein the oligonucleotide (3) is complementary to the other end of the single-stranded target DNA and thus a three component, double stranded assembly comprising oligonucleotide (1)-target DNA-oligolnucleotide (3)-liposome is formed on the transducer.

Thus, according to Patolsky, the oligonucleotide of the liposome hybridizes with the target analyte DNA. The oligonucleotide of the liposome does not, as required by claim 1, bind

to a surface-immobilized linker comprising an oligonucleotide, or a vesicle-attached linker comprising an oligonucleotide.

The technique of Patolsky is principally an improvement methodology for amplifying the sensing of a target DNA captured to a surface by additional binding of labeled liposomes. The present invention, on the other hand, is directed to multilayered structures of lipid vesicles having a bioactive compound associated with the vesicles in order, for example, to study interactions of the bioactive compounds, such as for example a membrane protein and its ligands. For this reason, it is an important feature that the multilayer structured is formed from hybridization of vesicle-attached oligonucleotide linkers. This feature admits improved control over the distance between sensitive biomolecules associated with the lipid vesicles and the surface. This is of particular advantage when using the structure for studying membrane proteins which often are liable for metal surface contacts. The oligonucleotide linkers thereby provide a useful tool to control and optimize such distances to the surface. Further, the oligonucleotide linkers are useful to tailor a pore size of the inventive multilayer structure which is of great advantage when predicting how the structure interacts with a complex solution of biomolecules, for example, with diffusive control.

Anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). In view of the failure of Patolsky to disclose that the oligonucleotide of the liposome binds to a surface-immobilized linker comprising an oligonucleotide, or a vesicle-attached linker comprising an oligonucleotide, Patolsky does not expressly or inherently describe each and every element as set forth in claim 1. Accordingly,

Patolsky does not anticipate claim 1, or claim 65 dependent thereon, and the rejection under 35 U.S.C. §102 has been overcome. Reconsideration is respectfully requested.

Claims 1, 8 and 63-65 were rejected under 35 U.S.C. §103(a) as being obvious and unpatentable over the Hamalainen et al U.S. Patent Publication No. 2002/0019019 A1, in view of the Keinanen et al U.S. Patent No. 6,235,535 and the Mirkin et al U.S. Patent No. 6,361,944. Claims 2 and 3 were rejected under 35 U.S.C. §103(a) as being obvious and unpatentable over these references and further in view of the Kataoka et al U.S. Patent Publication No. 2005/0079195 A1, while claim 5 was rejected under 35 U.S.C. §103(a) as being obvious and unpatentable over these references and further in view of the Brederhorst et al WO 02/081739 A2.

The Examiner asserted that Hamalainen teaches a biosensor with a sensor surface comprising a hydrogel matrix coating coupled to a top surface of the sensor surface, wherein the hydrogel matrix coating has a plurality of functional groups and at least two different liposomes (vesicles) are bonded to the plurality of functional groups at discreet and non-contiguous locations on the hydrogel matrix coating of the sensor surface. The Examiner further asserted that it would have been obvious to employ liposomes associated with membrane proteins since Keinanen teaches that such liposome structures can be used as recognition surfaces in biosensors, and to employ the immobilization method of Mirkin, in which vesicles are mobilized on a surface via hybridization of linker oligonucleotides. The Examiner relied on Kataoka as disclosing a coated support surface comprising multi-layer micelle (vesicles/liposomes), on a support surface for use in biomedical applications, and on Brederhorst as teaching linkers such as oligonucleotides can be attached to vesicles via a covalent bond using a functional group.

These rejections are traversed and reconsideration is respectfully requested. Applicants submit that the cited combinations of references provide no apparent reasoning for one of ordinary skill in the art to combine their teachings to result in a multilayer structure as recited in claim 1.

More particularly, Hamalainen discloses at paragraphs [0070] – [0079] the structure and preparation of a sensor surface. A hydrogel matrix is provided with a coating having a plurality of functional groups, with two different types of liposomes bonded to the functional groups via a lipophilic substance such as a substance comprising an alkyl chain having from 12 to 24 carbon atoms, for example, stearyl amine. Hamalainen specifically employ a CM5 sensor chip in a BIACORE 3000 Biosensor. However, Applicants find no teaching by Hamalainen of surface immobilized linkers serving to build several vesicle layers or that such vesicles include bioactive compounds, as defined in claim 1.

On the other hand, Keinanen discloses a fluorescence-based immunoassay method for the detection of an analyte. Receptor molecules which are labeled with a fluorophore and anchored to and freely mobile on a lipid membrane are aggregated with an analyte to be detected. At column 2, lines 4-30 relied upon by the Examiner, Keinanen simply reviews the prior art of lipid bilayers. However, one of ordinary skill in the art would have no motivation to modify the structure of Hamalainen in view of Keinanen since Hamalainen already employs liposomes and Keinanen relates to a relatively unrelated technology.

Mirkin discloses at column 5, lines 1-26 relied upon by the Examiner, a structure similar to that of Patolsky wherein a nucleic acid to be detected is contacted with a substrate having oligonucleotides attached thereto. The oligonucleotides have a sequence complementary to a first portion of the target nucleic acid and once the nucleic acid is bound to the substrate through

hydridization, it is contacted with liposomes having oligonucleotides attached thereto which are complementary to a portion of a sequence of the nucleic acid, whereby hybridization of the liposome oligonucleotide occurs. An aggregate probe having an oligonucleotide is then contacted with the assembly and upon attachment of the aggregate probe oligonucleotides to the liposomes as a result of hydrophobic interactions, a detectable change is observed. The target nucleic acid is therefore required for the assembly and Mirkin does not disclose, as required by claim 1, binding a vesicle attached oligonucleotide linker to either vesicle attached oligonucleotide linkers of other vesicles or directly with surface-immobilized oligonucleotide linkers.

Neither Kataoka nor Brederhorst resolve the deficiencies of Hamalainen, Keinanen and Mirkin. That is, Kataoka describes a lipid vesicle surface (micelles) to be used for drug delivery. This disclosure is completely unrelated to the fields of Hamalainen, Keinanen and Mirkin, and is similarly unrelated to the multilayer structures of the present invention. The evidence of record fails to establish why one of ordinary skill in the art would have found it obvious to combine any of the teachings of Kataoka with Hamalainen, Keinanen and Mirkin. Bredehorst (WO '739) was discussed in detail in Applicants' previous Amendment. As discussed therein, Bredehorst (WO '739) also discloses a technology similar to Patolsky in that a "sandwich structure" is formed (see Fig. 4) wherein captured analyte DNA is contacted with reporter liposomes to generate such a structure. However, Bredehorst (WO '739) fails to teach a multilayer structure as recited in claim 1.

In determining patentability under 35 U.S.C. §103, it is necessary to determine whether there was an apparent reason to combine the known elements of the prior art in the fashion of the claims at issue, *KSR International Co. v. Teleflex, Inc.*, 550 US 398, 418 (2007). In view of the

disparate teachings of the cited prior art and the failure of any of the cited references to teach or suggest a multilayer structure wherein a portion of the vesicles are directly attached to the structure by binding surface-immobilized linkers with vesicle-attached linkers and a portion of the vesicles are attached to the structure by binding vesicle-attached linkers to vesicle-attached linkers of other vesicles, so as to provide the structure with two or more vesicle layers, wherein binding of one linker to another linker is mediated through hybridization of the linker oligonucleotides, the cited combinations of references do not provide one of ordinary skill in the art with any apparent reason to combine the known elements of the prior art in the fashion of the claims at issue, and particularly in the fashion of the multilayer structure of claim 1. Thus, the cited combinations of references do not render the multilayer structures of claim 1, 5, 8 and 63-65 obvious and the rejections under 35 U.S.C. §103 have been overcome. Reconsideration is respectfully requested.

Claims 1-5, 8 and 63-65 were also rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-22 of co-pending application Serial No. 10/590,877. Although this is a provisional rejection, Applicants traverse the rejection on the basis that the present claims 1, 5, 8 and 63-65 are patentably distinct from claims 1-22 of the co-pending application. That is, as noted above, the present claims are directed to a biologically-functional, surface-immobilized multilayer structure which comprises a plurality of vesicles sufficiently spaced apart from said surface, wherein a portion of the vesicles are directly attached to the structure by binding surface-immobilized linker oligonucleotides with vesicle-attached linker oligonucleotides and a portion of the vesicles are attached to the structure by binding vesicle-attached linkers to vesicle-attached linkers of other vesicles, so as to provide the structure with two or more vesicle layers. Claims 1-22 of the co-pending application recite an

oligonucleotide having at least two hydrophobic anchoring moieties capable of being attached to a lipid membrane. The oligonucleotide structure of the co-pending application increases the stability of a linker attached to a lipid membrane by using a hydrophobic anchoring unit and is not required by and does not render obvious the multilayer structure of lipid vesicles according to the present claims. Accordingly, withdrawal of the obviousness-type double patenting rejection is respectfully requested.

It is believed that the above represents a complete response to Official Action, and places the present application in condition for allowance. In the event there are any outstanding issues relating to this application, the Examiner is urged to telephone the undersigned to efficiently resolve the same. Reconsideration and an early allowance are requested.

Please charge any fees required in connection with the present communication, or credit any overpayment, to Deposit Account No. 503915.

Respectfully submitted,

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